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Original Research

Efficacy and safety of mesenchymal stem cell therapies for ischemic stroke: a systematic review and meta-analysis

Zhiyuan Shen[1,2,3], Xian Tang[4], Yaxin Zhang[1], Yicun Jia[1], Xin Guo[1,2,3], Xiaosu Guo[1,2,3], Junqiang Bao[1,2,3], Xiongwei Xie[1,2,3], Yuan Xing[1,2,3,*], Jun Xing[4,*], Shujuan Tian[1,2,3,*]

[1]Department of Neurology, The First Hospital of Hebei Medical University, Shijiazhuang, Hebei 050030, People's Republic of China,
[2]Department of Neurology, Hebei Hospital, Xuanwu Hospital, Capital Medical University, Shijiazhuang, Hebei 050030, People's Republic of China,
[3]Neuromedical Technology Innovation Center of Hebei Province, Shijiazhuang, Hebei 050030, People's Republic of China,
[4]Department of Rehabilitation Medicine, The First Hospital of Hebei Medical University, Shijiazhuang, Hebei 050030, People's Republic of China

[*]Corresponding author: Shujuan Tian, MD, Department of Neurology, The First Hospital of Hebei Medical University, Shijiazhuang, Hebei 050030, People's Republic of China (57203005@hebmu.edu.cn); Jun Xing, MD, Department of Rehabilitation Medicine, The First Hospital of Hebei Medical University, Shijiazhuang, Hebei 050030, People's Republic of China (56901734@hebmu.edu.cn); or, Yuan Xing, MD, Department of Neurology, The First Hospital of Hebei Medical University, Shijiazhuang, Hebei 050030, People's Republic of China (58803030@hebmu.edu.cn).

Abstract

Background: The efficacy and safety of mesenchymal stem cells (MSCs) in the treatment of ischemic stroke (IS) remains controversial. Therefore, this study aimed to evaluate the efficacy and safety of MSCs for IS.

Methods: A literature search until May 23, 2023, was conducted using PubMed, EMBASE, the Cochrane Library, and the Web of Science to identify studies on stem cell therapy for IS. Interventional and observational clinical studies of MSCs in patients with IS were included, and the safety and efficacy were assessed. Two reviewers extracted data and assessed the quality independently. The meta-analysis was performed using RevMan5.4.

Results: Fifteen randomized controlled trials (RCTs) and 15 non-randomized trials, including 1217 patients (624 and 593 in the intervention and control arms, respectively), were analyzed. MSCs significantly improved patients' activities of daily living according to the modified Rankin scale (mean difference [MD]: −0.26; 95% confidence interval [CI]: −0.50 to −0.01; $P = .04$) and National Institutes of Health Stroke Scale score (MD: −1.69; 95% CI: −2.66 to −0.73; $P < .001$) in RCTs. MSC treatment was associated with lower mortality rates in RCTs (risk ratio: 0.44; 95% CI: 0.28-0.69; $P < .001$). Fever and headache were among the most reported adverse effects.

Conclusions: Based on our review, MSC transplantation improves neurological deficits and daily activities in patients with IS. In the future, prospective studies with large sample sizes are needed for stem cell studies in ischemic stroke. This meta-analysis has been registered at PROSPERO with CRD42022347156.

Key words: clinical efficacy; ischemic stroke; mesenchymal stem cells; safety.

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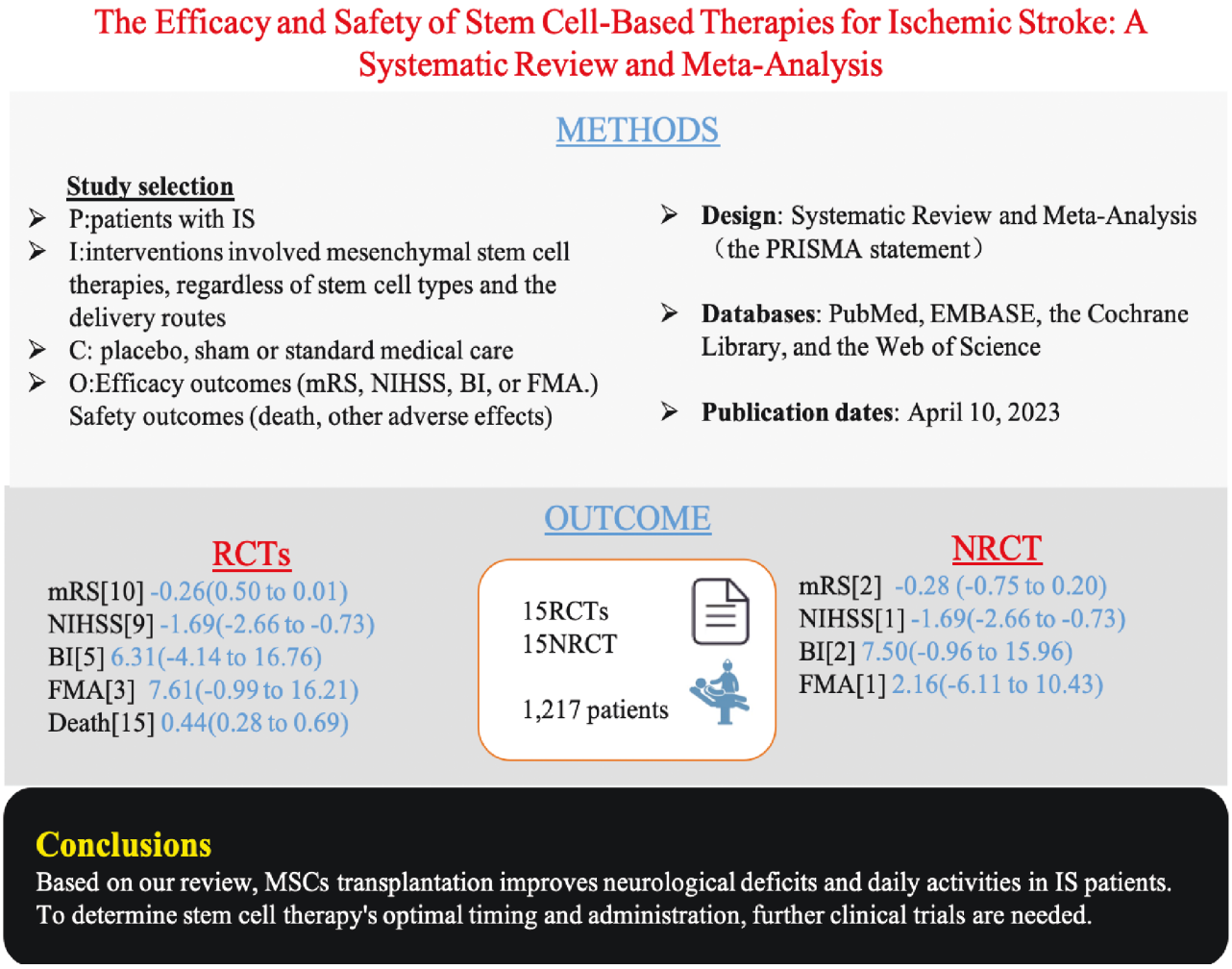
Graphical Abstract



Significance statement

There was no increase in adverse events associated with MSC therapy. Moreover, MSC therapy can improve neurological function and daily functioning in patients with IS; however, the benefits are still limited. Currently, MSC treatments for IS are still in their infancy, and the participants are limited. Future research should prioritize prospective studies with large sample sizes in the field of stem cell research for ischemic stroke.

Background

Stroke, the second-leading cause of death and disability, affects not only the patients but also their families and society at large.[1,2] Ischemic stroke (IS) is the most common stroke subtype, accounting for 60%-70% of all strokes.[3,4] Timely reperfusion is currently the most effective treatment for patients with IS.[5] The recovery of function and reorganization of the brain can be improved with reperfusion and rehabilitation; however, their effects are often limited.[6,7] Previous studies have demonstrated a poor prognosis with recombinant tissue plasminogen activator (rt-PA) and endovascular therapy for several reasons. First, the thrombolysis time window is too short and not suitable for all patients.[8,9] Second, hypoperfusion is common, and recanalization does not equal reperfusion.[10] Third, even with recanalization, more than half of the patients have a poor prognosis.[11] Therefore, more effective treatments are needed to improve the prognosis for patients with IS.

Mesenchymal stem cells (MSCs) have recently gained popularity for use in neuroregenerative therapy. MSCs, originally discovered by Friedenstein in 1974,[12] are highly heterogeneous cells that can be isolated from bone marrow, adipose tissue, umbilical cords, and placenta. In general, MSCs exert beneficial effects through immunomodulatory, regulatory, and paracrine mechanisms.[13,14] Many studies have demonstrated the safety and efficacy of stem cells to treat IS[15]; Nevertheless, the findings derived from various stroke scales exhibit inconsistencies,[16,17] and a lack of a dependable and authoritative protocol for MSCs in the management of IS persists. Therefore, thorough scientific investigation is required to determine the optimal selection of MSCs from various sources, treatment dosage, timing of treatment initiation, method of administration, and overall treatment approach. Therefore, this meta-analysis aimed to evaluate the efficacy and safety of MSCs for IS and determine the optimal conditions for treatment.

Methods

This study is registered with the International Prospective Register of Systematic Reviews, PROSPERO: CRD42022347156. The PRISMA checklist is available as Supplementary Materials.

Eligibility criteria

Inclusion criteria for the studies were as follows: (1) Studies on patients with IS assessed with computed tomography or magnetic resonance imaging, regardless of the phase. (2) In all interventions, MSC therapies were used, regardless of stem cell types and delivery routes. (3) The efficacy outcomes measured by the modified Rankin scale (mRS), the National Institutes of Health Stroke Scale (NIHSS), the Barthel index (BI), or the Fugl-Meyer motor scale (FMA), and safety outcomes were reported.

Exclusion criteria were as follows: (1) The outcome data could not be retrieved. (2) The report was a follow-up, case report, preclinical trial, literature review, or included patients with other diseases.

Search strategy

Clinical studies were identified by searching the PubMed, Cochrane Library, EMBASE, and Web of Science electronic databases from inception to July 22, 2022. The subject words used in the search strategy included "ischemic stroke," "brain ischemia," "mesenchymal stem cell," and "cell- and tissue-based therapy." The complete search strings are shown in the Supplementary Material. There was no language restriction. Clinical trials were selected as a result. On May 23, 2023, before the final analysis, the search was rerun to find more studies, although none were eligible.

Selection and study extraction

Investigators independently screened all citations by title and abstract in pairs. After retrieving the full texts of these studies, 2 investigators independently screened them for inclusion. The extracted contents were as follows: (1) basic information for each study, including author (year), study type, country, eligibility criteria (mean NIHSS), time from onset to infusion, patients included (experimental/control group), intervention (donor origin, tissue origin, fresh or frozen), dose, administration route, frequency, comparison, other treatments, follow-up (after intervention), and outcome measures; and (2) mean score and SD after treatment for each assessment used to measure functional recovery alone. We chose to use the first data point after treatment. A third investigator was consulted if there was a disagreement about inclusion. The reasons for exclusion were noted and reported for all studies.

Quality of assessment

The quality of the included studies was assessed using the Cochrane Handbook for Systematic Reviews of Interventions.[18] For non-randomized controlled trials (NRCT), the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) was used. Risk of Bias 2 (RoB 2) was used for randomized controlled trials (RCT). A third reviewer resolved any biases and disagreements of the reviewers.

Statistical analysis

Each study's intervention effects are summarized using random-effects meta-analysis with mean differences (MD; continuous outcomes). Risk ratios (RR; dichotomous outcomes) were used to calculate 95% CIs and 2-sided *P*-values for studies that used the same intervention and comparator with the same outcome measure. Studies of different types (RCTs or NRCTs) were pooled separately. The chi-square test and I^2 statistic were used to assess study heterogeneity. An I^2 value of more than 50% indicated substantial heterogeneity. Using a standardized MD and two-sided *P*-value for each outcome, heterogeneity was determined using subgroup analysis. A sensitivity analysis was performed to evaluate the influence of each study. We used funnel plots to assess the publication bias. Statistical analysis was performed using Review Manager 5.4 (RevMan 5.4, The Cochrane Collaboration, Copenhagen, Denmark).

Results

Search results

A total of 3163 records were initially identified; duplicate records were excluded from 141 records, and 2928 references were excluded owing to irrelevance. After full-text reviews of the remaining 81 references, we excluded 51 studies that did not meet the criteria. Finally, we included 30 studies[19–48] involving 1217 participants in this review (Figure 1).

Study characteristics

The included studies were published between 2005 and 2023 from 13 countries. Thirty studies were included, 15 RCTs and 15 NRCTs, 29 in English and one in Chinese. A sample size ranging from 4 to 210 patients was used in the study, and the follow-up lasted from 90 days to 5 years. Most studies were carried out in the US ($n = 10$) and China ($n = 5$). The most common studies had NIHSS scores ≥7. In 22 studies, the stem cells used were autologous; in 8, the stem cells were allogeneic. Intravenous injection was the most common mode of administration. Supplementary Table S1 shows the characteristics of the included studies.

Quality assessment of studies

For RCTs,[19-33] the RoB 2 tool was used. Among 13 RCTs, "random" was mentioned, and a method of generating random sequences was described. The overall study quality level was medium-to-high, with 6 of the 15 studies classified as having a high risk of bias in at least one domain (Figure 2). For NRCTs,[34–48] the ROBINS-I was used. Six of the 14 studies had a high risk of bias in at least one domain, indicating a moderate study quality (Figure 2).

Efficacy outcomes

mRS

As of the end of the follow-up (90 days to 5 years), 13 RCTs[19,21-32] and 2 NRCTs[37,46] reported the mRS. However, in 3 RCTs,[20,28,33] the mRS could not be extracted, and our email inquiries to the corresponding authors were unanswered. Participants in the stem cell group had improved outcomes in RCTs (MD: −0.26, 95% CI: −0.05 to −0.01, $P = .04$; Figure 3A) but not in NRCTs (MD: −0.28, 95% CI: −0.75 to 0.20, $P = .26$; Figure 4A).

NIHSS

The NIHSS score was reported by 11 RCTs[19,22-29,31,32] and 2 NRCT[37,48] at the end of the follow-up (180 days to 4 years).

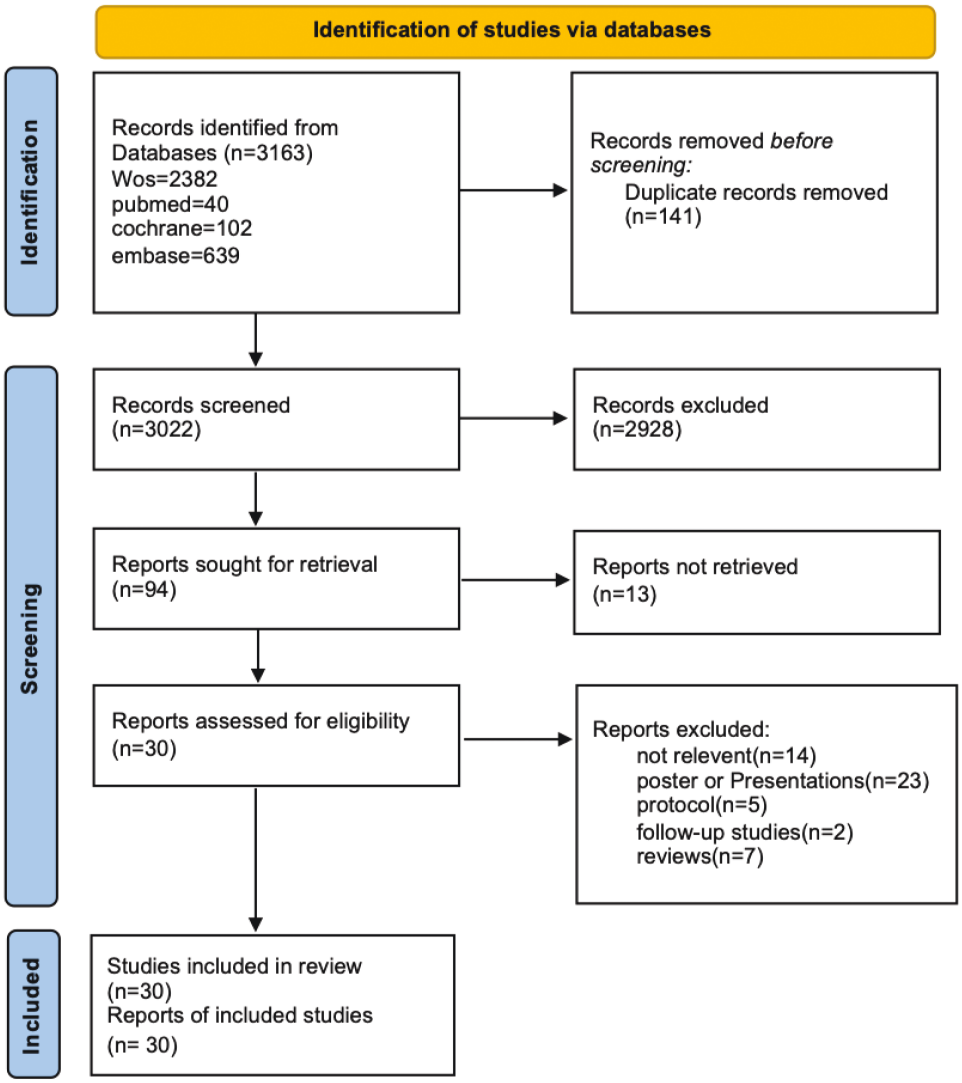


Figure 1. Flow diagram of study selection.

In 2 RCTs[24,28] and 1 NRCT,[48] the NIHSS score could not be extracted, and our email inquiries to the corresponding authors went unanswered. The stem cell group had a significantly better outcome than the controls in RCTs (MD: −1.69, 95% CI: −2.66 to −0.73, $P < .001$; Figure 3B), but no beneficial outcomes in NRCTs (MD: −2.71, 95% CI: −5.54 to 0.12, $P = .06$; Figure 4B).

BI

The BI was reported by 8 RCTs[19,23-25,27-29,31] and 2 NRCTs[36,37] at the end of the follow-up (180 days to 4 years). In 3 RCTs,[24,25,28] the BI data could not be extracted, and we did not receive a response from the corresponding authors. The stem cell groups had no beneficial outcomes compared to the RCTs' control groups (MD: 6.31, 95% CI: −4.14 to 16.76, $P = .24$; Figure 3C). The stem cell groups had an improved trend in NRCTs (MD: 7.50, 95% CI: −0.96 to 15.96, $P = .08$; Figure 4C), but this difference was not statistically significant.

FMA

Three RCTs[20,30,33] and one NRCT[36] reported the FMA at the end of the follow-up (90 days to 6 months). The FMA data in one NRCT was only available for the upper limbs. Stem cell groups had no beneficial outcomes compared with control groups in RCTs (MD: 7.61, 95% CI: −0.99 to 16.21, $P = .08$; Figure 3D). In NRCTs, stem cell groups showed an improved trend (MD: 2.16, 95% CI: −6.11 to 10.43, $P = 0.61$; Figure 4D); however, no statistical significance was observed.

Safety outcomes

Death

Death was reported by all RCTs[19-33] and NRCTs[34–48] at the end of the follow-up (90 days to 5 years). The stem cell group showed a significantly lower mortality rate than controls in RCTs (RR: 0.44, 95% CI: 0.28-0.69, $P < .001$; Supplementary Figure S1).

Adverse effects

Adverse effects were concerned by all RCTs[19-33] and NRCTs[34–48] at the end of the follow-up (90 days to 5 years; Supplementary Table S2). In 3 RCTs and one NRCT, no adverse effects were reported. Among cell-related adverse effects, headache and fever were the most common. Additionally, seizures, nausea, and vomiting were reported as adverse effects related to the cells. The findings indicated a higher prevalence of psychiatric

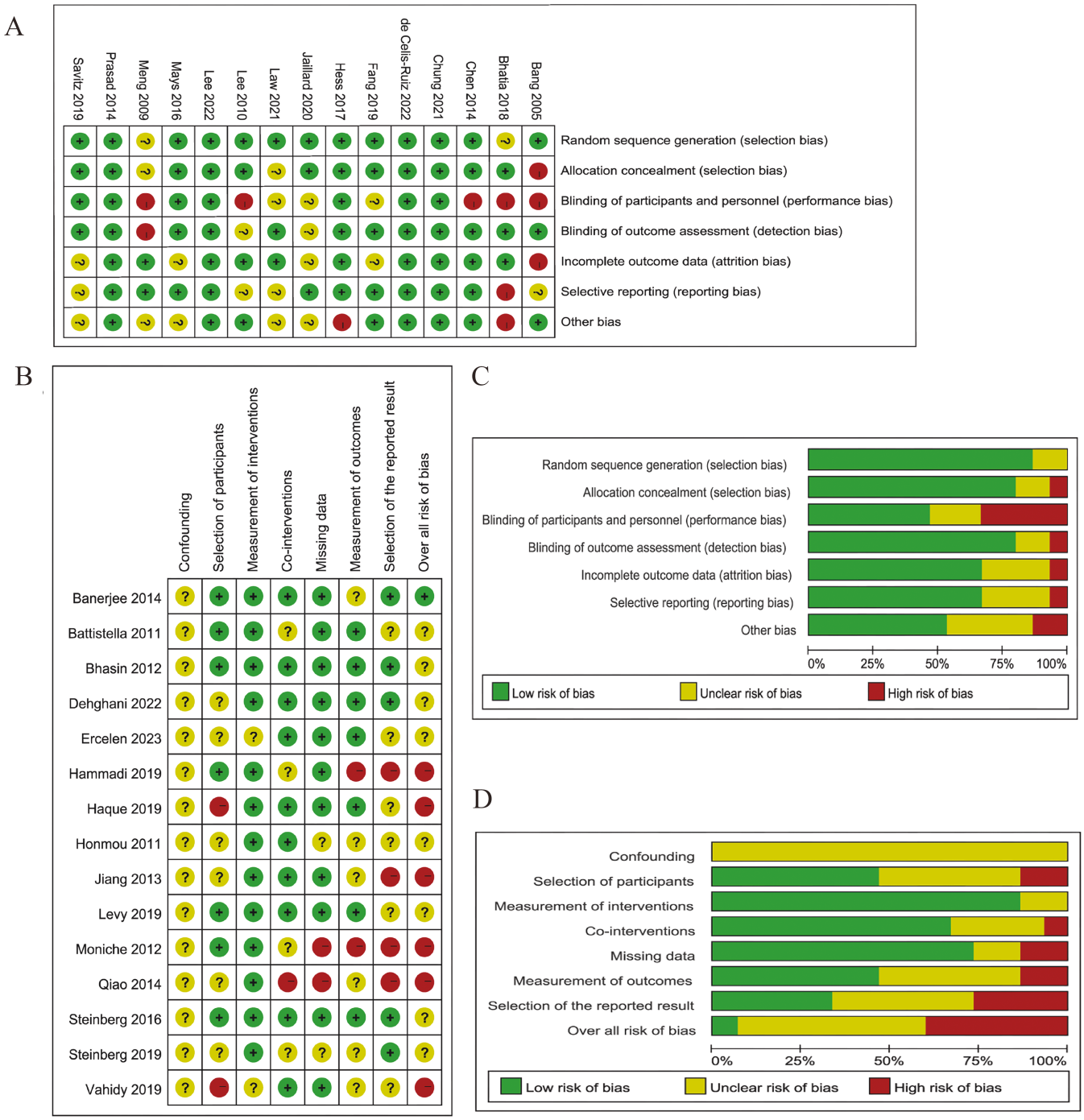


Figure 2. Plots showing risk of bias for (A, C) RCTs and (B, D) NRCTs.

disorders and fever in the stem cell group, as well as elevated enzyme levels in 3 studies, although no statistically significant differences were observed (Supplementary Figure S2).

Subgroup analyses

We conducted a subgroup analysis to determine the difference in magnitude of the impact of arterial and intravenous delivery on IS outcomes. We found that intravenous administration improved the NIHSS score (MD: −1.38; 95% CI: −2.36 to −0.40; $P < .001$), while arterial administration did not (Table 1).

Subgroup analysis of MSCs administration at different stages after stroke suggested that MSCs had a positive effect on NIHSS score (MD: −2.34, 95% CI: −3.51 to −1.17, $P < .001$) and BI (MD: 20.54, 95% CI: 4.46-36.62, $P = .01$) when administered 2 weeks to 3 months after IS onset. MSCs also improved patients' mRS (MD: −0.60, 95% CI: −0.90 to −0.30, $P < .001$) and NIHSS score (MD: −3.20, 95% CI: −4.52 to −1.88, $P < .001$) when administered >3 months after IS (Table 1). However, when administered within 2 weeks after IS, there was no significant improvement in the patient's mRS, NIHSS, and BI.

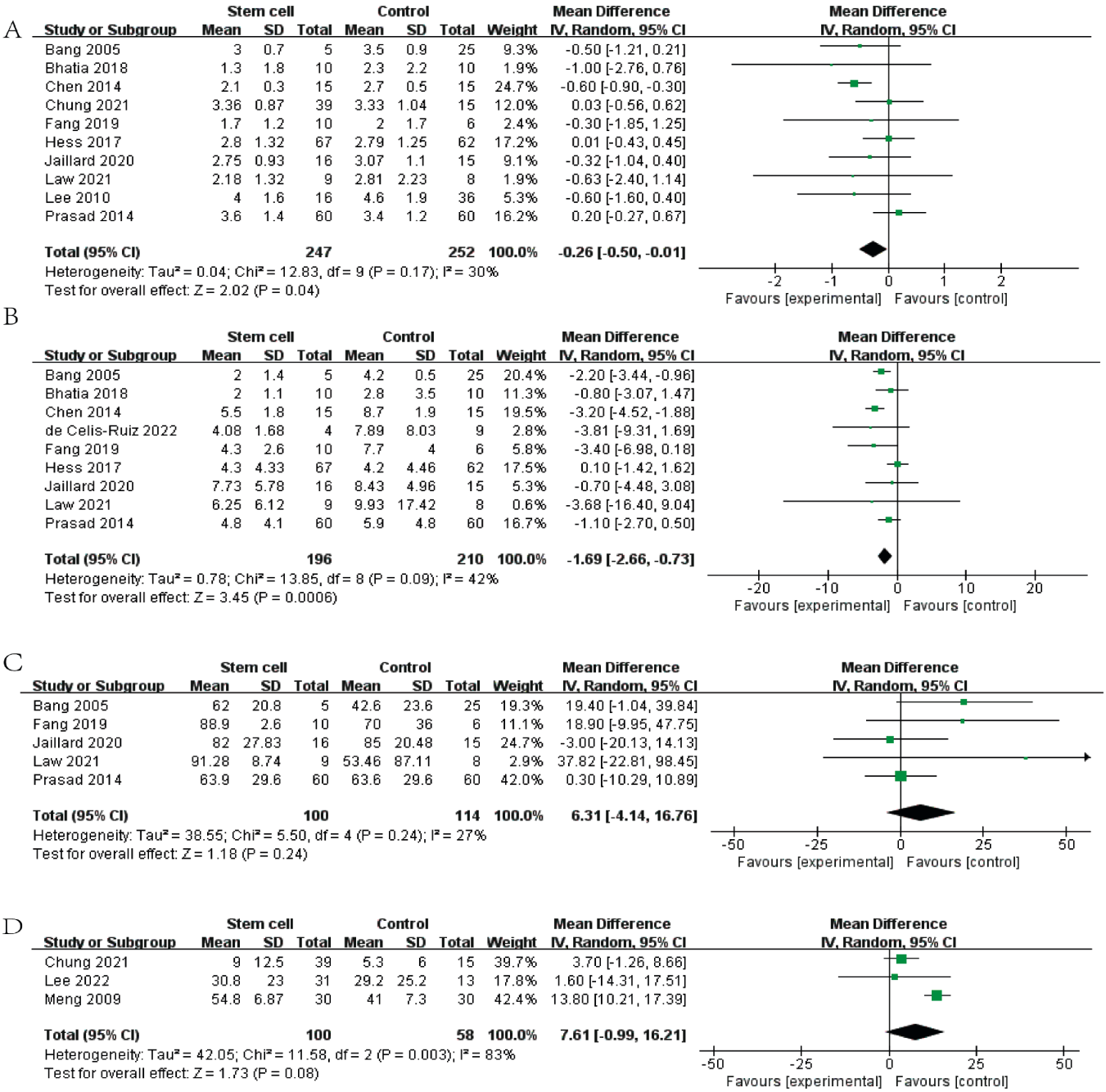


Figure 3. Forest plots showing effect size of RCTs on (A) mRS, (B) NIHSS, (C) BI, and (D) FMA.

We further performed a subgroup analysis on the origin of cells (autologous or allogeneic), and the results suggested that autologous cells had better efficacy in NIHSS (MD: −2.10; 95% CI: −2.88 to −1.33; $P < .001$) and mRS score (MD: −0.31; 95% CI: −0.58 to −0.04; $P = .02$) improvements (Table 1). However, no improvement in mRS and NIHSS scores was observed in the study of allogeneic cells.

Sensitivity analysis and publication bias

Due to the limited NRCTs data, we only conducted sensitivity analysis and funnel analysis on RCTs. Sensitivity analysis showed that, after excluding studies with the smallest and largest sample sizes, only the mRS score changed, while NIHSS, BI, and FMA remained unchanged, suggesting that our results had relatively good robustness (Supplementary Figures S8 and S9). Funnel plots showed no evidence of publication bias (Supplementary Figure S10).

Discussion

Our systematic review and meta-analysis evaluated the safety and efficacy of MSC therapy for IS in clinical settings. To the best of our knowledge, this is the largest clinical meta-analysis in this field. Our review included 15 RCTs and 15 NRCTs. Based on the available evidence, MSCs therapy can be used safely in clinical settings. Our review found that MSCs

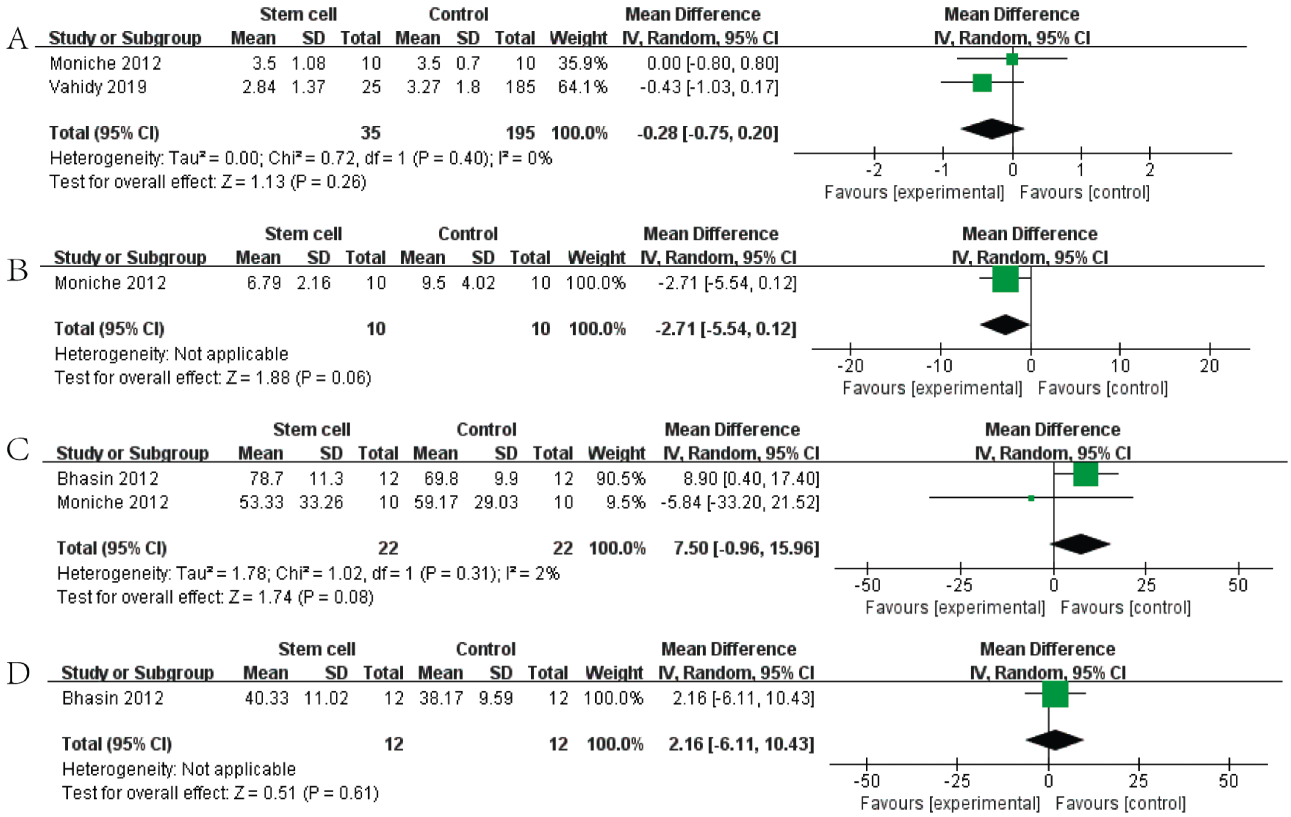


Figure 4. Forest plots showing effect size of NRCTs on (A) mRS, (B) NIHSS, (C) BI, and (D) FMA.

therapies improved the NIHSS, mRS, and mortality rates in RCTs. FMA and BI were slightly higher in the stem cell group, but the difference was not significant.

In clinical trials, NIHSS, mRS, BI, and FMA are commonly used measures for assessing stroke. In our review, NIHSS and mRS results in RCTs indicate that stem cell-based therapies have better outcomes. Stem cell group had slightly better in BI and FMA but without significant difference. However, there was no statistically significant difference among the 4 scales in NRCTs. Another meta-analysis showed that stem cell-based therapies were related to better outcomes when measured by NIHSS and BI in RCTs and by BI in NRCTs.[16]However, a separate meta-analysis revealed significant statistical disparities across all 4 scales, suggesting that the effectiveness of stem cell transplantation exceeded that of conventional control therapies.[17] Despite the inclusion of a greater number of studies in our meta-analysis compared to other studies, the limited quantity of studies assessing BI and FMA remains a potential factor contributing to the lack of statistically significant difference observed in our study. Furthermore, it is crucial to note that patients exhibiting similar NIHSS or mRS scores may display varying scores on BI or FMA. Consequently, variations in baseline BI or FMA scores may influence the assessment of outcomes based on these measures, particularly in cases with a restricted sample size. Research involving high-quality RCTs and large samples is needed on a future basis. Furthermore, the studies included in our review exhibit substantial variability in follow-up durations, spanning from 90 days to 5 years. This disparity may have contributed to discrepancies in scale scores and could potentially elucidate the statistical variances observed in certain variables that were not corroborated by our research findings.

Our research on the safety of MSC treatment is comparable to another review,[16] with fever and headache being the most common adverse reactions with no risk of serious complications, such as tumorigenicity or toxicity, observed. In the RCTs conducted in our study, it was noted that the mortality rate in the stem cell group was lower compared to the control group. The findings of our study align closely with those of a prior meta-analysis.[49] However, due to the lack of a control group or no deaths in the studies, the subgroup analysis was not applicable to NRCTs. Interestingly, the findings indicated a higher incidence of psychiatric disorders and fever in the stem cell group compared to the control group. Three studies reported elevated enzyme levels, although no statistically significant difference was observed. Further clinical research should focus on these adverse reactions.

It is important to note that stem cell-based therapies are affected by many factors in clinical practice. A variety of cell types were used in our review, including bone marrow stem cells (BM-MSCs), umbilical cord MSCs, peripheral blood hematopoietic stem cells, endothelial progenitor cells, and adipose-derived MSCs, among which BM-MSCs was the most widely used. However, the limited number of MSCs produced by bone marrow requires invasive methods, and their proliferation and differentiation potential decline with age.[50] According to previous studies, umbilical cord MSCs have stronger proliferation activity than BM-MSCs, adipose tissue, or dental pulp.[51] To determine the best MSC sources for clinical applications, future studies must determine the consistency and the mechanisms by which MSCs originate from different sources and identify the most effective and least harmful MSCs in IS.

Table 1. Subgroup analysis of different factors of MSCs for the treatment for ischemic stroke in RCTs.

Subgroup factors	Variable	Effect size			
		MD (95% CI)	*P*-value	Heterogeneity (*P*-value)	*P*-value
Different administration route	*mRS*				
	IA	−1.00(−2.76 to 0.76)	.27	NA	.41
	IV	−0.08(−0.32 to 0.15)	.49	0% (.67)	
	NIHSS				
	IA	−0.80(−3.07 to 1.47)	.49	NA	.002
	IV	−1.38(−2.36 to −0.40)	.006	22% (.26)	
	BI				
	IA	NA	NA	NA	.24
	IV	6.31(−4.14 to 16.76)	.24	27% (.24)	
Different stages after stroke	*mRS*				
	<2 W	−0.12(−0.49 to 0.25)	.52	0% (.45)	<.001
	2 W-3 M	−0.52(−1.03 to 0.00)	.05	0% (.99)	
	>3 M	−0.60(−0.90 to −0.30)	<.001	NA	
	NIHSS				
	<2 W	−0.39(−1.56 to 0.78)	.51	0% (.56)	.002
	2 W-3 M	−2.34(−3.51 to −1.17)	<.001	0% (.81)	
	>3 M	−3.20(−4.52 to −1.88)	<.001	NA	
	BI				
	<2 W	−3.00(−20.13 to 14.13)	.73	NA	.14
	2 W-3 M	20.54 (4.46-36.62)	.01	0% (.85)	
	>3 M	NA	NA	NA	
Different tissue origin	*mRS*				
	autologous	−0.31(−0.58 to −0.04)	.02	25% (.22)	.04
	allogeneic	0.01(−0.43 to 0.45)	.96	NA	
	NIHSS				
	autologous	−2.10(−2.88 to −1.33)	<.001	8% (.37)	<.001
	allogeneic	0.10(−1.42 to 1.62)	.90	NA	
	BI				
	autologous	6.31(−4.14 to 16.76)	.24	27% (.24)	.24
	allogeneic	NA	NA	NA	

In our review, the autologous MSCs group improved neural function, while the allogeneic MSCs group did not. This may be due to the lack of research on allogeneic MSCs. While autologous MSCs are the safest option, allogeneic MSCs also have many advantages. First, autologous MSCs need to be cultured and expanded for a long time, which limits their application in the acute phase of IS, while allogeneic MSCs can be obtained and expanded more quickly from cryobanks. Second, most patients with IS take antiplatelet or anticoagulant drugs, and conducting bone marrow puncture surgery for culturing autologous bone marrow mesenchymal stem cells while on these medications may elevate the likelihood of postoperative bleeding at the puncture site. Allogeneic MSCs from healthy donors do not pose this issue. Third, the physiological properties of MSCs are affected by age.[52]

We reviewed various delivery methods, including intravenous, intraarterial, and intraparenchymal. Intravenous and intraarterial delivery was preferred in the acute to subacute phase, while intraparenchymal delivery was preferred in the chronic phase. Intravenous injection was the most common delivery method owing to its relatively low trauma and simple operation technique. However, the intravenous method is limited in that it must reach the artery through the systemic veins and then cross the blood-brain barrier. Due to this, most MSCs reside in peripheral organs such as the lungs, liver, spleen, and kidneys. Consequently, only 4% of MSCs injected intravenously reach ischemic brain tissue. Thus, the best route for administration still remains unclear. Our subgroup analysis found that the intravenous administration group improved NIHSS scores while the arterial administration group did not. However, this may be related to the limited number of studies in the arterial administration group.

A previous meta-analysis showed that the best method of administration was intracerebral, followed by intraarterial, and finally intravenous.[53] This is similar to our research results. In our subgroup analysis, after removing the only study with intracerebral implantation, the stem cell group did not produce a positive result on mRS, however, not all patients can undergo neurosurgery. Craniotomies can be avoided with stereotactic technology, but they may also damage brain parenchyma and the blood-brain barrier, causing neuronal damage, inflammation, hemorrhages, and epilepsy. Therefore,

a clinical evaluation of intracerebral administration is necessary. MSCs administered intranasally can enter the brain directly through the olfactory nerve, thereby bypassing the blood-brain barrier.[54] Additionally, intranasal MSCs reduced infarct volume and improved neural function in preclinical studies.[55] It is also worth noting that administering a reduced dosage of MSCs intranasally can achieve the same effects as intracranial injections.[56] Its advantages are non-invasive, simple to use, and can be administered repeatedly. Humans, however, have smaller olfactory bulbs than rodents; thus, clinical trials are needed to determine if patients with IS can benefit from intranasal MSCs similarly to animal models.

Our subgroup analysis found that in the RCTs, mRS, and NIHSS were significantly effective in the chronic phase of stroke, but the effect was not significant within 2 weeks after stroke, similar to a previous meta-analysis.[57] However, there were too few studies to draw definitive conclusions. A meta-analysis of a preclinical study involving 141 articles showed that the comprehensive neurological function score of the 2-7 days group was significantly improved compared to the group of 12-24 hours and >7 days. Additionally, the 0-6 hours and 2-7 days groups showed no significant difference, suggesting that these may be the best administration times after IS.[58] More high-quality clinical trials are warranted to determine the optimal time for stem cell infusion in patients with IS.

A clear understanding of the exact mechanisms underlying the beneficial effects of MSCs in IS is still lacking in preclinical and clinical studies. The data supporting the transplantation of MSCs to differentiate and replace damaged nerve cells after transplantation is very scarce. When MSCs are transplanted into the cortex around the infarcted area, they are able to express neuron-specific markers; however, differentiated neurons are immature. A more important problem is that they lack voltage-gated ion channels that are necessary for generating action potentials.[59] Increasing evidence suggests that immune regulation, neuroprotection, angiogenesis, and neural circuit reconstruction may be the main mechanisms of MSCs in treating IS.[60]

Recently, therapies based on stem cells for IS have been improved to increase efficacy and reduce adverse effects. Several strategies, including gene transformation or overexpression, pretreatment, combination therapy, and MSC extracellular vesicle transplantation, are available.[61–67] An 18-patient chronic stroke cohort was transplanted with SB623 cells and the BM-MSCs transfected with the Notch-1 gene; after 24 months of treatment, clinical outcomes showed significant improvements.[68] Additionally, a combination of electroacupuncture and MSCs transplantation significantly improved motor function in mice after cerebral infarction.[69] In addition, MSC transplants in combination with minocycline reduced the size of infarcts and improved neurological function, potentially due to minocycline's ability to enhance MSC neurogenesis and angiogenesis.[70]

Preclinical studies have suggested that the benefits of neurological function and the dosage of MSCs may be in an inverted U shape.[53] This proposes that a large dose of MSCs given through arteries or veins will cause microvascular obstruction or thrombosis, reducing brain or organ perfusion. The optimal dose needs to be determined by clarifying the relationship between effectiveness and safety. For inverted U-shaped vertices, more clinical and preclinical studies are needed.

Research on the relationship between the frequency of stem cell administration and the efficacy of IS is limited. However, our study did not find that the more frequent the administration, the better the efficacy. Although this may largely be the reason for the lack of relevant research at present. A study from South Korea suggested that MSCs can protect against ischemic injury, and the frequency of injections is more important than the dosage of MSCs[71]. Further research is warranted to clarify the correlation between administration frequency and stem cell improvement in IS efficacy.

Our meta-analysis has some limitations. First, we conducted a comprehensive literature review using sensitive search algorithms and manual searches on meeting records and reference lists. We are, therefore, unlikely to miss out on relevant clinical trials. However, we could not obtain additional unpublished data and are aware that a substantial amount of information is unavailable to the public. Thus, we cannot rule out publication bias. Second, most studies were judged to have at least some concerns about the risk of bias for primary outcomes. Different cell types, cell numbers, delivery pathways, time windows, and medical and rehabilitation therapies in the study can all affect the efficacy of stem cells. Third, due to limited data, subgroup analysis related to dosage could not be conducted.

Conclusions

This systematic review and meta-analysis provide a comprehensive, up-to-date evaluation of MSC therapy for IS safety and efficacy. There was no increase in adverse events associated with MSC therapy. Moreover, this meta-analysis indicated that MSC therapy can improve neurological function and daily functioning in patients with IS; however, the benefits are still limited. Currently, MSC treatments for IS are still in their infancy, and the participants are limited. Future research should prioritize prospective studies with large sample sizes in the field of stem cell research for ischemic stroke.

Author Contributions

Zhiyuan Shen and Xian Tang conceptualized and designed the study. Yaxin Zhang, Jun Xing, and Shujuan Tian coordinated and supervised the systematic review; Zhiyuan Shen, Xian Tang, and Xin Guo selected the articles, extracted the data, and assessed the risk of bias. Xian Tang performed the data analysis. Yaxin Zhang, Yicun Jia, Junqiang Bao, and Xiongwei Xie assessed the certainty of the evidence and interpreted the results. Zhiyuan Shen and Xian Tang drafted the initial version of the manuscript. All authors critically reviewed and approved the final manuscript as submitted. Zhiyuan Shen and Xian Tang contributed equally to this work.

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played no role in the design of the study; the collection, analysis, or interpretation of data; or in writing the manuscript.

Ethics approval

This project was approved by the Ethics Committee of the First Hospital of Hebei Medical University (approval number: 20210349; date of approval: March 12, 2021).

Conflict of interest

The authors declared no potential conflicts of interest.

Data availability

Study data are provided as supplementary material.

Supplementary Material

Supplementary material is available at *Stem Cells Translational Medicine* online.

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